Fifth National Forum on Biomedical Imaging in Oncology
January 29-30, 2004 – Bethesda, Maryland

Presented by: National Cancer Institute, Food and Drug Administration, Centers for Medicare and Medicaid Services and National Electrical Manufacturers Association

Sponsored by: National Institutes of Health/Foundation for Advanced Education in the Sciences (NIH/FAES)

Introduction and Objectives
The National Forum on Biomedical Imaging in Oncology (NFBIO) was created to facilitate partnerships with the imaging industry and government agencies to address new biomedical opportunities and challenges in oncology, and to focus on the regulatory, coverage, and reimbursement issues for more developed and established technologies. During the 2004 NFBIO, speakers focused on the potential implications for in vivo imaging of a variety of technical advances including molecular imaging, nanotechnology, combination products, optical technologies and quantum dots, phage display, and computer-aided detection and diagnosis. In addition, the NCI, Food and Drug Administration (FDA), and Centers for Medicare and Medicaid Services (CMS) summarized progress made on issues since the 2003 NFBIO.

A major goal of this meeting is to foster the advancement of more accessible and accurate imaging technology and movement of interventions into the clinic.

Introductory Remarks From Industry
The Medical Division of the National Electrical Manufacturers Association (NEMA) leads and assists the diagnostic imaging and therapy systems industry in defining domestic and international policy, regulations, legislation, standardization, and guidance on medical devices. NEMA values the scientific interactions between industry, government agencies, and academia and has supported the NFBIO since its inception. NEMA is developing a new Web site at www.medicaldiagnosticimaging.com to inform the media, Congress, employers, and international organizations of the benefits of diagnostic imaging in an effort to balance the hype on the high cost of diagnostic imaging.

Forum Issues: Update from Food and Drug Administration (FDA) [presentation slides]
The FDA perspective on developing new imaging technology was presented. The FDA is responsible for ensuring that a drug or device is effective and safe. When a specific claim is made for a device or drug, the manufacturer must submit clinical evidence for FDA approval. New technology is changing the accuracy of the way medicine is practiced and adding value to existing technology. Tremendous potential exists for the use of imaging during drug development, e.g., to study drug-target interaction, determine dose and exposure to adjacent organs, and follow how a surrogate marker behaves with an effective drug in a trial. The Center for Drug Evaluation and Research (CDER) recently convened a cross-agency working group for the use of imaging as a biomarker in drug development. In addition, CDER will develop a guidance on micro dose approach in early clinical development.

Forum Issues: Update from Centers for Medicare and Medicaid Services (CMS) [presentation slides]
An overview of the coverage and reimbursement process for the Medicare program was given. Authority for CMS to make decisions for Medicare is based on the Social Security Act, which states that items and services must be reasonable and necessary. Recent efforts have focused on making the decision process for coverage more transparent, understandable, and open to the public. National Coverage Decisions (NCDs) have been issued for specific oncological FDG-PET indications and image-guided percutaneous breast biopsy among other diagnostic tests. Several NCD requests are currently under review. CMS will engage the industry in developing guidance documents on the coverage and review of evidence processes. This collaboration should enhance the quality of clinical research to support evidence-based Medicare coverage decisions for biomedical imaging tests.

Forum Issues: Update from National Cancer Institute (NCI) [presentation slides]
An overview of NCI and National Institutes of Health initiatives and resources available for researchers and developers involved in the field of cancer imaging technology was presented. NCI's current investment in cancer imaging, including budget, contract support, grant initiatives, and platforms to interact with other Institutes, government agencies, and with technology developers in academia and industry was discussed. Accelerating the development of imaging technologies is the goal of the Interagency Council on Biomedical Imaging in Oncology. This Council, composed of staff from the NCI, FDA, and CMS, continues to serve as a sounding board for investigators and manufacturers attempting to take emerging medical imaging technology to market. Clinical trials are a major focus, and have emphasized the detection of the most common cancers - lung, breast and colon cancer. The National Lung Screening Trial (NLST), which was launched in September 2002, and randomized individuals to spiral CT versus CXR, enrolled its target goal of 50,000 current or former smokers this month. Researchers will continue to contact participants annually to monitor their health until 2009, with the goal of discerning whether either modality decreases lung-cancer related deaths. In late 2003, the Digital Mammography Imaging Screening Trial (DMIST) enrolled its target goal of 49,500 women in the United States and Canada. All women received digital and standard mammograms to ascertain the performance characteristics of the imaging technologies in detecting breast cancer. Clinically-annotated images from these trials will be available to the research community. A CT colonography screening trial is currently under development. Treatment trials are also being designed, and a clinical trial in a cancer with rising incidence, hepatocellular carcinoma, will be evaluating radiofrequency ablation. The NCI/FDA Interagency Oncology Task Force was initiated in May 2003 to enhance the efficiency of clinical research and the scientific evaluation of new cancer drugs, and is currently evaluating the potential of using imaging as a biomarker.

New Vistas Lecture - Clinical Needs and Future Challenges for Molecular Imaging [presentation slides]
Moving beyond the dominant paradigm of multistep tumorigenesis, cancer as a field defect, and equal lethal potential of all cancer cells/tumors may help researchers identify new methods for the early detection of breast cancer and depict the anatomy of the breast and its lesions with more accuracy. The breast should be studied as a collection of ductal systems with their own physiology and anatomy. Can we image the progression/regression of breast cancer in vivo? Imaging could offer better ways for identifying ductal trees for surgery planning, monitoring ductal pathology and effects of treatment, identifying milk duct orifices, directing ductal ablation or intraductal drug delivery, and finding markers in fluid or cells.

The Potential of Proteomics
Research into the cancer cell continues to evolve and reveal more about the genetic pathways that cause cellular processes to change in cancer. Protein fragments, either free or attached to large carrier proteins in serum and plasma, are being investigated to detect cancer at its earliest stages. The early detection of cancer has improved survival rates in several tumor types. Once cancer is detected, imaging can be used to find the location of the tumor(s). Serum and plasma are full of interesting proteins, but need to be sampled over a huge diagnostic range. New technologies such as mass spectrometry have permitted a new science of diagnostics for protein identification and quantification. Dr. Hartwell advocates developing a transdisciplinary network of researchers to systematically identify peptides and proteins critical to cancer processes using a model organism, with the ultimate goal of having thousands of molecular targets for imaging agents.

Ovarian Cancer - An Ideal Model for Molecular Imaging Technologies [presentation slides]
A clinical overview of ovarian cancer and the potential role of molecular imaging was presented. Ovarian cancer is treatable, but seldom curable since residual tumors remain undetected after debulking. In addition, treatment becomes less effective as disease progresses. Current technology for the intraperitoneal imaging is inferior. Intra-peritoneal molecular imaging could provide important prognostic and therapeutic information.

Optical Spectroscopic Technologies for *In Vivo* Imaging [presentation slides]
Spectroscopic imaging can aid in the diagnosis and management of neoplasia by guiding biopsy and providing the opportunity for real-time diagnosis and treatment. Preliminary clinical studies have shown that the combination of diffuse reflectance spectroscopy, light scattering spectroscopy, and intrinsic fluorescence spectroscopy provides a powerful tool for spectroscopic diagnosis and diagnostic imaging. In addition, Raman spectroscopy has the potential to become a valuable diagnostic tool by providing a means for *in vivo* chemical analysis of lesional tissues. In the future, spectroscopic data may be correlated with cellular and molecular biological data to provide information about the natural history of neoplastic lesions and to monitor response to treatment *in vivo*.

Quantum Dots for *In Vivo* Imaging [presentation slides]
Quantum dots are nanometer-sized semi conductors (crystals) that glow when stimulated with ultraviolet light. Latex beads filled with these crystals can be designed to bind to specific DNA sequences. Quantum dots can be combined within a single bead to create probes that release distinct colors and intensities of light. An overview of highly luminescent and stable quantum dots and their potential implications in molecular profiling of single cells and tissue specimens was presented. The development of quantum dots has implications for the fields of diagnostics, molecular imaging, molecular profiling, pharmacogenomics, and drug discovery. Images of quantum dot-labeled cancer cells in live animals were shown. In the future, we can expect to see quantum dots integrated with ‘smart’ nanostructures for non-invasive sensing, imaging, and treatment of cancer.

Basics of Phage Display for Imaging Agent Development [presentation slides]
Phage display uses bacteria and bacterial viruses known as phage to display random DNA sequences encoding peptides/proteins. The use of phage display in screening for novel high-affinity ligands and their receptors has been crucial in functional genomics and proteomics. The peptides can function as imaging or therapeutic targeting agents. The use of genetically engineered bacteriophage libraries that encode peptides with intrinsic radiometal-chelation or fluorescent sequences has the potential to expedite the direct selection of peptides for cancer imaging.

Current Patient Management with Molecular Imaging [presentation slides]
Imaging is being used to detect and stage cancer, guide cancer treatment selection, and evaluate early treatment response. The trend of more personalized therapy is driving the clinical use of molecular imaging for the assessment of therapeutic targets and identification of resistance factors to match therapy to tumor biology. Imaging can capture heterogeneity of target expression and measure the *in vivo* effect of drug therapy on the target, i.e. receptor antagonism or change in target expression. New imaging agents to accomplish these goals are undergoing preliminary testing in patients in many centers, and will hopefully soon be entering multi-center trials for more comprehensive testing and validation of the utility in guiding patient management.

The Potential of Nanotechnology in Cancer Diagnosis and Treatment [presentation slides]
Nanotechnology is the creation of useful materials, devices, and systems through the manipulation of matter on this miniscule scale. Tools developed through nanotechnology may be able to detect disease in a very small amount of cells or tissue. They may also have the potential to enter and monitor cells within a living body. Researchers hope that nanotechnology will be used in prevention and control, early detection and proteomics, imaging diagnostics, multifunctional therapeutics, nanosystems for quality life, and training. An overview of the NCI nanotechnology plan was provided. The nanotechnology 'road show' is being taken to the NCI Comprehensive Cancer Centers and nanotechnology programs are being developed within NCI. A nanotechnology lab at NCI is under development in collaboration with the FDA.

"The Nanolab": The Potential for Technology Integration
Systems biology is an approach in which the digital information of the genome, acted upon by environmental cues, generates the many molecular signatures of gene and protein expression, as well as other more phenomenological experimental observations. Dr. Heath is putting together a nanolab that integrates nanotechnology with systems biology. Nanowires, microfluids, and molecular imaging are being used to investigate the cell and protein signature expression. This technology is being used to probe not only biological molecules from single cells, but all genomic and proteomic expression and interactions. This technology holds promise as tool for developing, using and testing molecules as probes that target proteins, DNA, and mRNA to test systems biology models, as well as providing molecular diagnostics and molecular therapeutics within a systems biology framework.

Contrast Ultrasound Imaging and Local Drug Delivery [presentation slides]
Ultrasound contrast agents (UCAs) are being used to improve the specificity of ultrasonic imaging. UCAs consist of a gas core that is encapsulated by a shell, typically constructed of a lipid or cross-linked albumin. UCAs are introduced into the blood stream and produce a very strong echo due to their compressible gas core. The detection of flow in small blood vessels is challenging since the echoes from blood are 100 times smaller than echoes from the surrounding tissue. Applications for the clinic include visualization of tumor vascularity, measurement of flow characteristics, differential diagnosis, guided biopsy, and therapy monitoring and delivery.

Compound Product: Digital Mammography with Integrated Ultrasound [presentation slides]
Full field digital mammography has been used for cancer imaging, staging, and detection. Several studies have revealed that screening with mammography has reduced breast cancer mortality. Ultrasound has been shown to significantly improve sensitivity and specificity over mammography alone, while mammography combined with ultrasound significantly improves staging. An overview of clinical research with this combined technology was provided along with a description of systems from General Electric, Fisher Imaging, and U-Systems. Cost, training, and patient acceptance are potential barriers to the implementation of this new technology.

Further clinical research, such as ACRIN trial 6666, is needed to further investigate the supplemental benefit of ultrasound when combined with mammography.

Computer-Aided Detection and Computer-Aided Diagnosis: Integration with Imaging
The quality of a radiologic examination depends on both the quality of the image acquisition and the quality of the image interpretation. Computer-aided technology has developed for medical imaging to improve the quality of image interpretation, overcome limitations of the human eye-brain system, and ease the task of analyzing vast amount of data for human interpretation. Computer-aided diagnosis (CAD) is a diagnosis made by a radiologist who takes into consideration the output from a computer analysis of an image. CAD has applications for the detection and diagnosis of lesions, as well as risk assessment of future disease. Computer-aided detection involves the use of computer output to direct a radiologist's attention to regions on a medical image that the computer deems to have features associated with cancer. Results from studies using computer-aided technology for detection and diagnosis of breast, lung, and colon cancers were discussed. This technology has been shown to improve the sensitivity for cancer detection and has the potential to improve the sensitivity and specificity of interpretation in the task of lesion classification. Observer study results on lesion classification have shown that use of computer-aided diagnosis has the potential to move the performance level of general practice radiologists up that of expert mammographers. Future applications include computerized cancer risk assessment and computerized image analysis to aid in prognosis.